

## REMARKS

### Formal Matters

Claims 1-10, 17-23 and 45-52 were examined and stand rejected.

Claims 5-8, 17, 20-23 and 46 have been canceled. Claims 1-4, 8-10, 18-19, 45 and 47 are pending after entry of the amendments set forth herein.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Support for the amendments to claims 1-4, 8-10, 18-19, 45 and 47 can be found throughout the specification, at, for example, page 54, lines 7-31 and page 55, lines 1-14. As such, no new matter has been added.

### Claim Objections.

Claim 2 was objected to under 37 C.F.R. § 1.75(c) because it was asserted that the claim is written in an improper dependent form. The Office Action alleges that Claim 2 fails to further limit the subject matter of a previous claim because “it’s unclear how [a screening marker] is different from the ‘selection marker’.”

Applicants disagree with the Examiner’s assertions and respectfully traverse this rejection. Applicants point to the specification of the instant application, which distinguishes a screening marker from a selection marker. A sequence coding for a screening marker, such as, for example, green fluorescent protein (GFP) may be included with a targeting construct so that cells that have undergone homologous recombination may be identified upon exposure to a fluorescent light (Page 10, lines 3-10). In particular, “cells that have undergone homologous recombination will have deleted the GFP gene and will not fluoresce.” (Page 13, lines 6-18). As such, a screening marker enables one skilled in the art to visualize cells that have undergone homologous recombination.

In comparison, a sequence coding for a selection marker, such as, for example, a neomycin resistance (*Neo'*) gene may be included with a targeting construct so that cells

that have undergone homologous recombination survive and/or grow under certain conditions (Page 7, lines 26-31). For example, cells that express a neomycin resistance gene are resistant to the compound G418, while cells that do not express the neo gene marker are killed by G418. The cells transformed with the targeting construct of the present invention may be subjected to treatment with an appropriate agent that selects against cells not expressing the selectable marker (Page 13, lines 6-18). As such, a selectable marker enables one skilled in the art to distinguish living from non-living cells.

According to the above-reference pages, the Applicants submit that the specification distinguishes a screening marker from a selection marker. Accordingly, the Applicants submit that the term “screening marker” limits the subject matter of Claim 1. Thus, it is argued that Claim 2 meets the requirements of 37 C.F.R. § 1.75(c) by further limiting the claim and as such, Claim 2 is a properly written dependent claim.

**Rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph.**

Claims 5-10, 17-23 and 45-52 have been rejected under 35 U.S.C. § 112, 1<sup>st</sup> paragraph because it is asserted in the Office Action that the specification, while being enabling for a homozygous knockout mouse comprising a homozygous disruption in the magnesium-dependent phosphatase gene wherein there is no functional magnesium-dependent phosphatase produced, and exhibiting phenotypic features including lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold relative to a wild-type mouse, does not provide enablement or adequate written description for a **any transgenic animal** with **any type** of disruption in any magnesium-dependent phosphatase gene and **any phenotype**, or how to make and use the invention with **any type** of cell.

Specifically, the Office Action asserts that the specification, while being enabling for a knockout mouse with a homozygous disruption in a magnesium-dependent phosphatase gene identified as SEQ ID NO: 1 wherein there is no functional magnesium-dependent phosphatase produced, and exhibiting phenotypic features including a lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold relative to a wild-type mouse, a method of making said mouse by introducing a knockout

construct into an embryonic stem cell, does not reasonably provide enablement or adequate written support for a transgenic mouse comprising **any type** of disrupted magnesium-dependent phosphatase gene having **any phenotype** other than a lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold and a method of making the knockout mouse by introducing a knockout construct into **any type** of cell.

Further, claims 1-10, 17-23 and 45-52 have been rejected under 35 U.S.C. § 112, 1<sup>st</sup> paragraph as containing subject matter which was not described in the specification as to reasonably convey to one skilled in the art that the inventor at the time the application was filed, had possession of the claimed invention. In particular, Office Action asserts that the specification “describes a single species of a magnesium-dependent phosphatase gene, the murine gene of SEQ ID NO: 1.” (Office Action, page 10)

With respect to both sets of claims rejected under 35 U.S.C. § 112, 1<sup>st</sup> paragraph, Applicants have adopted Examiner’s suggested modifications, or addressed Examiner’s rejection, by: (1) inserting SEQ ID NO: 1 after the term “magnesium-dependent phosphatase gene;” (2) inserting homozygous to describe the type of disruption in the magnesium-dependent phosphatase gene; (3) reciting the specific type of cell (i.e., mouse ES cell) into which the knockout targeting construct is introduced; and (4) inserting phenotypic language into the pending amended claims such that the transgenic mouse having a homozygous disruption in magnesium-dependent phosphatase exhibits a lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold.

In light of the foregoing, Applicants submit that the rejections of the above-cited claims under 35 U.S.C. § 112, first paragraph, both as to enablement and written description, are overcome in view of the amendments, claim cancellations, and remarks set forth herein. The Examiner is thus respectfully requested to withdraw these rejections.

**Rejection under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph.**

Claims 1-4, 9-10, 23 and 52 have been rejected under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Examiner asserts that the terms “selectable marker,” “screening marker,” or “selection marker” renders the claims indefinite because it is unclear how a marker protein can be part of a vector construct. Examiner has recommended the use of the term “selectable marker gene,” “screening marker gene,” or “selection marker gene.”

Applicants have amended the claims according to Examiner’s recommendation.

Examiner asserts that the difference between the terms “screening marker” and “selection marker” is unclear. As stated earlier in the “Claim Objections” section of this response, Applicants disagree with the Examiner’s assertions and respectfully traverse this rejection. Applicants point to the specification of the instant application, which distinguishes a screening marker from a selection marker. A sequence coding for a screening marker, such as, for example, green fluorescent protein (GFP) may be included with a targeting construct so that cells that have undergone homologous recombination may be identified upon exposure to a fluorescent light (Page 10, lines 3-10). In particular, “cells that have undergone homologous recombination will have deleted the GFP gene and will not fluoresce.” (Page 13, lines 6-18). As such, a screening marker enables one skilled in the art to visualize cells that have undergone homologous recombination.

In comparison, a sequence coding for a selection marker, such as, for example, a neomycin resistance (*Neo'*) gene may be included with a targeting construct so that cells that have undergone homologous recombination survive and/or grow under certain conditions (Page 7, lines 26-31). For example, cells that express a neomycin resistance gene are resistant to the compound G418, while cells that do not express the neo gene marker are killed by G418. The cells transformed with the targeting construct of the present invention may be subjected to treatment with an appropriate agent that selects against cells not expressing the selectable marker (Page 13, lines 6-18). As such, a selectable marker enables one skilled in the art to distinguish living from non-living cells. According to the above-reference pages, the Applicants submit that the specification distinguishes a screening marker from a selection marker.

Examiner asserts that, in claims 1-4 and 10, the arrangement of the targeting construct is unclear. Accordingly, Applicants have amended the above-cited claims to identify the location of the selectable marker gene and screening marker gene in the target construct.

Examiner asserts that claims 9 and 23 are indefinite with respect to the word “derived.” It is suggested by the Examiner to replace “derived” with “isolated.” Accordingly, Applicants have adopted the Examiner’s suggestion.

Examiner asserts that claim 52 lacks a proper antecedent basis. In light of the cancellation of claim 52, Applicants submit that the rejection is moot.

**Rejection under 35 U.S.C. § 103(a).**

Claims 1-8 and 10 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mansour et. al. (1988, *Nature*, vol. 336, No. 24, pages 348-352) in view of Kato et. al (1994, *Gene*, vol. 145, pages 311-312) and Travis *et al.*, 1997, *Proc. Natl. Acad. Sci. U.S.A.*, 94:11055-11060 (“Travis”). Applicants respectfully traverse this rejection. However, in view of the cancellation of claims 5-7 and in view of the amendments to the pending claims, Applicants submit that the rejection under 35 U.S.C. § 103 is no longer relevant.

In order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: there must be some suggestion or motivation to modify a primary reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) **must teach or suggest all the claim limitations.** See MPEP §2143.

As amended, the pending above-cited claims describe phenotypic abnormalities for the transgenic mice including a lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold.

According to the Examiner, Mansour teaches a strategy for targeted disruption of the *hprt* and proto-oncogene *int-2* in mice embryonic stem cells, and subsequent generation of knockout mice. The disclosure of Mansour specifically relates to a general method for isolating embryonic stem cells containing a targeted mutation in an

endogenous gene. More particularly, Mansour teaches the targeted disruption of the *hprt* gene and the proto-oncogene *int-2* in mouse embryonic stem cells by homologous recombination using targeting constructs specific for these genes.

Kato et. al., as characterized by the Examiner, discloses the cloning of a mouse magnesium-dependent phosphatase gene. The Examiner relies on the teachings of Gao to provide motivation to disrupt the magnesium-dependent phosphatase gene.

Travis et. al., as characterized by the Examiner, discloses that human magnesium-dependent phosphatase is involved in cystic fibrosis pathogenesis and asserts that human magnesium-dependent phosphatase is a good target for developing inhibitors that have therapeutic value for cystic fibrosis.

However, neither Mansour, Kato nor Travis alone or in combination, teaches all of the limitations as presently claimed. Mansour provides no disclosure or teaching of how to make a magnesium-dependent phosphatase gene knockout mouse. In particular, Mansour does not disclose a transgenic mouse comprising a disruption in a magnesium-dependent phosphatase gene, wherein the transgenic mouse exhibits a specific phenotype, particularly a phenotype of a lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold, as presently claimed. Likewise, Kato does not provide any teaching or suggestion relating to targeted disruptions in any gene, particularly in a magnesium-dependent phosphatase gene. More particularly, the disclosure of Kato fails to provide any teaching or suggestion that relates to transgenic mice or cells, and in particular to those transgenic mice and cells as recited in the pending claims. Likewise, Travis merely discloses a desirability to study human magnesium-dependent phosphatase because of an association with cystic fibrosis pathogenesis.

Taken together, the disclosures of Mansour, Kato nor Travis are devoid of any teaching or suggestion of disrupting the magnesium-dependent phosphatase gene, and in particular, are deficient of any teachings or suggestions of the transgenic mice and cells as recited in the pending claims. More particularly, the disclosures of Mansour, Kato nor Travis alone or combined, do not teach or suggest in any way transgenic mice comprising a disrupted magnesium-dependent phosphatase gene, wherein such transgenic mice exhibit a phenotype, and in particular exhibit a phenotype of a lung abnormality, elevated

white blood cells, increased anxiety and increased pain threshold as claimed by the present invention.

As the obviousness rejection is no longer relevant as result of the cancellation of claims 5-7 and amended claims 1-4 and 8-10 are not obvious in view of the teachings of Mansour, Kato and Travis, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

**Rejection under Non-Statutory Double Patenting.**

Claims 17-23 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 51-54 and 56 of co-pending Application No. 09/815,935.

The Office Action suggests that “a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome [the] . . . provisional rejection.” Although Applicants contend that the present application and cited Application No. 09/815,935 are patentably distinct from each other, Applicants have adopted the Examiner’s suggestion and have provided a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) and 37 C.F.R. § 3.73(b). Applicants submit that the rejection is overcome by this terminal disclaimer and respectfully request that this rejection be withdrawn.

Therefore, Applicants submit that rejection of the above-cited claims under the judicially created doctrine of obviousness-type double patenting, is overcome in view of the terminal disclaimer and remarks set forth herein. The Examiner is thus respectfully requested to withdraw these rejections.

**Conclusion.**

Applicants submit that all of the pending claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

Application No. 09/972,741  
Deltagen Docket No. R-723CIP

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1271.

Respectfully submitted,  
DELTAGEN, INC.

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